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Ondansetron and pregnancy: Understanding the data

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Abstract

Nausea and vomiting of pregnancy (NVP) is a common condition affecting 75% of pregnant women. NVP generally commences early in the first trimester, peaking in severity between 7 and 12 weeks and in over 90% symptoms will have abated by week 20. Thus, the time when women are most likely to have NVP and require treatment coincides with the embryonic period when there is maximum susceptibility to any teratogenic risk. Following the thalidomide tragedy of 55 years ago there is a particular awareness and sensitivity about these potential risks, especially in relation to any medication used to treat NVP. Despite several studies showing no clear benefits of ondansetron over other NVP treatments such as doxylamine, and the paucity of safety data, the off-label prescribing and use of ondansetron to treat NVP has increased significantly worldwide. Albeit based on limited human pregnancy data, ondansetron has not been associated with a significantly increased risk of birth defects or other adverse pregnancy outcomes. This review attempts to highlight some of the difficulties in interpreting the available data and the need to follow practical guidelines regarding treatment of NVP.

Keywords

Nausea and vomiting of pregnancy, hyperemesis gravidarum, ondansetron, birth defects, medications

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Background

Nausea and vomiting of pregnancy (NVP) is a common condition that affects approximately 75% of pregnant women. About 25% of women have nausea only while almost 50% of women experience both nausea and vomiting.[1]

NVP and the more severe hyperemesis gravidarum (HG) can result in weight loss, dehydration, and metabolic disturbances including acidosis, hypokalaemia, hyponatraemia and ketonuria. Prolonged symptoms can result in B group vitamin deficiencies and rarely-reported complications such as oesophageal rupture, peripheral neuropathy and Wernicke's encephalopathy. The clinical course and severity of NVP appears to correlate with levels of human chorionic gonadotropin (hCG) and thus women with twin pregnancies and hydatidiform moles are at higher risk of symptoms, while it is less common in smokers as well as older and multiparous women, possibly on the basis of a smaller placental volume. Around two-thirds of multiparous women with NVP had symptoms in a previous pregnancy.[1]

NVP per se has been reportedly associated with a lower risk of miscarriage. Infants of mothers with NVP who lose weight in early pregnancy have lower mean birth weight and are more likely to be $<10^{th}$ percentile for birth weight than those whose mothers' weight remained static or increased.[2]

In around one-third of women, NVP causes significant psychosocial morbidity and can affect normal functioning both at home and in the workplace.[3,4] Some women may consider or even terminate an otherwise wanted pregnancy because of intractable NVP symptoms.[5] While the majority of women can be managed conservatively, a proportion require medication and an even smaller number (<1%) require hospitalisation for intravenous fluids and therapy to manage hyperemesis gravidarum.[4]

The symptoms of NVP generally commence early in the first trimester (between 3 and 8 weeks amenorrhoea) with a peak in severity between 7 and 12 weeks. For the majority of women (60%), symptoms have resolved by the end of the first trimester and 91% will have abated by week 20.[1] Thus, the time when the majority of women are most likely to be symptomatic and require treatment coincides with the embryonic period (time of organogenesis), which is the time of maximum susceptibility to any teratogenic risk. Following the thalidomide tragedy of 55 years ago there is a particular awareness and sensitivity about these potential risks, especially in relation to any medication used to treat NVP.

The American Congress of Obstetrics and Gynecology (ACOG) and Australia's Therapeutic Guidelines have published guidelines for the pharmacological management of NVP, recommending a stepwise approach, commencing with pyridoxine (vitamin B6), doxylamine (and ginger) and then, depending on the presence or absence of dehydration, adding intravenous fluids as well as agents such as promethazine, metoclopramide, ondansetron and methylprednisolone.[6,7]

Ondansetron is a serotonin $5HT_3$ receptor antagonist that was originally developed for use as an anti-emetic in patients following surgery, chemotherapy and radiotherapy. Ondansetron can be given orally or intravenously in doses up to 8 mg three to four times daily. Reported side effects include headache, constipation, diarrhoea and fatigue[8] and there are theoretical concerns about potential QT prolongation and torsade de pointes as well as serotonin syndrome[9] although no reports of these complications with regard to treatment of NVP were identified in the literature.

In a small pilot study, Sullivan et al.[10] showed no benefit of IV ondansetron over IV promethazine in treating hospitalised patients with hyperemesis gravidarum. Despite this and other studies showing no clear benefits over other NVP treatments, and the paucity of safety data the off-label prescribing and use of ondansetron to treat NVP has increased significantly worldwide, including Australia, where data from Western Australia in the period 2002–2005 when there were almost 97,000 births showed that ondansetron was dispensed to 251 pregnant women, and the numbers of ondansetron prescriptions dispensed increased five-fold between 2000 and 2005.[11]

There are numerous websites in the United States urging women who took ondansetron during pregnancy and whose babies have birth

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Table 1. Shepard's amalgamation of criteria for proof of human teratogenicity with specific reference to ondansetron.[14]

Criterion	In relation to ondansetron
1. Proven exposure to agent at a critical time(s) in prenatal development (prescriptions, physicians records, dates)	No – extremely difficult with mainly registry data and many with uncertain exposure timing or exposure after embryogenesis.
2. Consistent findings by at least 2 high-quality epidemiological studies a) control of confounding factors b) sufficient numbers (adequate power) c) exclusion of positive and negative bias factors d) prospective studies if possible e) relative risk of 6 or more (?)	No Only 1 prospective study with relatively small numbers. Mainly case-control retrospective studies.
3. Careful delineation of clinical cases. Description of a specific defect or syndrome if present is very helpful	No specific malformation syndrome has been described.
4. Rare environmental exposure associated with a rare defect	No – ondansetron is not a rare exposure and the defects of concern are cardiac septal defects and orofacial clefts which are not considered rare.
5. Teratogenicity in experimental animals important but not essential	No – Intravenous doses up to 4 mg/kg/day did not result in any adverse effects on fertility or fetal anomalies in rats and rabbits.
6. The association between exposure and teratogenic effect should make biologic sense (biological plausibility)	No – Evidence in rat and mouse whole-embryo culture that serotonin plays a role in cardiac development. Theory about prolongation of QT interval and cardiac arrhythmias resulting in embryonic cardiac hypoperfusion and reperfusion anomalies such as septal defects. However, these have not been demonstrated in animal models.
7. Proof in an experimental system that the agent acts in an unaltered state	Ondansetron has not been definitively shown to cross the placenta – although its molecular weight of 293 and elimination half-life of 4.5 h suggest it would. However extensive hepatic metabolism may limit the amount of parent drug crossing the placenta.

defects to contact them and file damages suits.[12,13] This does not necessarily indicate that the drug is a teratogen but has certainly increased awareness and raised concerns about exposure to ondansetron during pregnancy.

Ondansetron and risks of birth defects

Animal studies have *not* shown an increased risk of infertility, birth defects or other adverse reproductive outcomes and there are limited data available about human pregnancy outcomes following exposure to ondansetron.

For any given agent it is difficult to categorically prove or disprove teratogenicity. Shepard devised 7 criteria (the first 3 being regarded as essential and 5–7 as being helpful but not essential) to prove teratogenicity and essentially ondansetron fails to meet any of these criteria (Table 1).

Sources of data and methodological considerations

Because of obvious ethical concerns, pregnant women cannot be included in randomised controlled studies looking at reproductive outcomes following medication exposures. Thus human pregnancy exposure data must be obtained from other, often indirect, sources. These include prospective observational studies, retrospective case-controlled studies, case reports and series, population prescription and birth defects registries, spontaneous drug company reports as well as drug company registries. While all of these data sources have some advantages and disadvantages, prospective cohort control studies are generally considered optimal in terms of quality of data, although they are expensive and time-consuming and require large numbers of exposed pregnancies to achieve satisfactory power and statistical significance. The answer to the question of whether or not a drug is a moderate teratogen is seldom answered by a single study and ondansetron is a good example of this phenomenon (Table 2).

Initial small case series and reports all included exposures only after organogenesis.[15–19] The first prospective study looking at the safety of ondansetron in pregnancy was a multicentre (Canada and Australia) cohort controlled e study which followed up 176 pregnancies with first trimester exposure to ondansetron and compared them to 176 women with NVP taking other antiemetics (disease-matched controls) and 176 non-exposed controls.[20]

Overall the rate of birth defects in the exposed group was no greater than the controls and there was no particular pattern of malformations, although there were 4 cases of genito-urinary anomalies (3 cases of hypospadias and 1 double urinary collecting system). Of note and in light of future concerns, there was only one case of a congenital cardiac defect, described as mild pulmonary stenosis (which is not a septal defect)

As can be seen from the table above, the most data about exposure to ondansetron during pregnancy has come from either retrospective case-controlled studies or has been derived from large prescription/birth defects databases and population cohorts which have inherent problems in their methodology as outlined below.

Databases which link prescriptions and birth defects are being increasingly used worldwide to determine pregnancy outcomes following exposures, although they were never designed or intended to assess drug safety. Gideon Koren, in an article entitled 'Scary Science: Ondansetron safety in pregnancy-Two opposing results from the same Danish Registry' highlights some of the pitfalls when trying to obtain and interpret pregnancy safety data from large population-based prescription and birth defects registries.[9]

Because they analyse large population datasets these studies have statistical power but nevertheless have significant methodological problems, including first and foremost, the assumption that just because a prescription was filled the medication was actually

Table 2. Summary of studies of ondansetron use during pregnancy.

Study	Design	Sample size	Results – major malformations	Comments
Guikontes et al.[15]	Case report	$n=1$ Exposure from 11-13/40	No anomalies	Healthy neonate
World MJ[16]	Case report	$n=1$ Exposure from 30–33/40	No anomalies	Mother with intercurrent renal disease Elective delivery at 36/40 Healthy neonate
Tincello et al.[17]	Case report	$n=1$ Exposure from 14–33/40	No anomalies	Healthy neonate delivered at 39/40
Siu et al.[18]	Case report	$n=1$ Exposed for 10 days from 12/40	No anomalies	3 previous TOP for hyperemesis gravidarum Gestational diabetes mellitus PPROM at 35/40 Healthy neonate
Einarson et al.[20]	Prospective comparative cohort	$n=176$ exposed, $n=176$ exposed to other anti-emetics, $n=176$ non-teratogen controls	No increase in major malformations (3.6%)	No difference in birth weight, GA at birth, rates of miscarriage, termination, LBW, stillbirth
Asker et al.[21]	Swedish Medical Birth Registry	$n=21$ exposed T1 $n=12$ exposed T1–T3 $n=12$ exposed T2–T3	No birth defects	Small numbers but 2 LBW, 1 SGA, 2 preterm birth
Anderka et al.[22]	National Birth Defects Prevention Study (NBDPS) Multi-site population based case -control study	4524 cases, 5859 controls 67.1% NVP and 15.4% ($n=621$) treated for NVP in T1 (all meds)	Overall no increased risks of birth defects Specifically increased risk of cleft palate (aOR = 2.37, 95% CI 1.18–4.76)	
Ferreira et al.[19]	Retrospective case series	$n=17$ live births, 16 pregnancies, (1 set of twins)	1 baby with ASD/VSD and ankyloglossia (but treatment only from 23 + 6/40) 1 mild hydrocele (ondansetron from 14/40) Extrarenal pelvis (ondansetron from 8 + 3/40)	Only 7 cases of exposure during organogenesis IUGR in twin pregnancy Transient tachypnoea of newborn
Pasternak et al.[23]	Retrospective population-based cohort Danish registry data- Medical Birth Registry, National Patient Register, National Prescription Registry	$n=1233$ T1 exposure $n=4932$ unexposed	No increase in major birth defects (2.9% in both exposed and unexposed groups OR 1.12; 95%CI 0.69–1.82)	No increase in other adverse pregnancy outcomes including miscarriage, stillbirth, low birth weight or prematurity
Andersen et al.[25]	Danish Nationwide Cohort Study 1997-2010 Data from Medical Birth Registry, National Hospital Register, National Prescription Register	$n=897,018$ births during study period $n=1248$ redeemed prescription for ondansetron in T1	58 (4.7%) had baby with congenital malformation after T1 prescription compared to 31,357 (3.5%) in unexposed group aOR of malformation after ondansetron was 1.3 (95% CI 1.0–1.7) and specifically aOR of 2.0 (95% CI 0.3–3.1) for cardiac defects	Metoclopramide use examined to rule out confounding by indication and no association with birth defects seen Still relatively small numbers and CI for cardiac defects includes 1

(continued)

Table 2. Continued

Study	Design	Sample size	Results – major malformations	Comments
Danielsson et al.[24]	Historical cohort 2004-2011 Swedish Medical Birth Register, Swedish Register of Prescribed Drugs	$n = 1349$ exposed in early pregnancy (899 exposed from <5 weeks – 9 weeks i.e. during organogenesis / 450 exposed 10–12 weeks)	No increase in birth defects overall Increased risk of cardiac defects (OR = 1.62, 95% CI 1.04–2.14) and specifically cardiac septal defects (RR = 2.05,95% CI 1.19–3.28)	Exposure to ondansetron identified by midwife interview (435 cases) and 914 from prescription register (less accurate data re actual ingestion, dose and gestational timing)
Colvin et al.[11]	Data from Western Australian Data Linkage System (WADLS) 2002–2005 including WA Birth Defects Registry, Midwives Notification System and National Prescribing Data (PBS)	96,968 births 251 exposed to ondansetron (263 offspring)	10 major birth defects (4.7%) in ondansetron group exposed in first trimester OR 1.2 (0.6–2.2)	Overall risk of birth defects not significantly increased and wide CI No details about specific malformations Exposure to ondansetron obtained from national prescribing data

T1, T2, T3: 1st trimester, 2nd trimester, 3rd trimester; ASD/VSD: atrial septal defect/ventricular septal defect; GA: gestational age at delivery; SGA: small for gestational age; LBW: low birth weight; TOP: termination of pregnancy; IUGR: intra-uterine growth restriction; NVP: nausea and vomiting of pregnancy; PPROM: prolonged premature rupture of membranes.

taken during the pregnancy. Frequently, they provide minimal or no details about the specific birth defects and thus no conclusions can be drawn with regard to patterns or trends seen regarding the types of birth defects identified following exposure to ondansetron, even assuming they all occurred in the critical period of organogenesis.

The relative paucity of cases of first trimester exposure is another significant problem. It is important to emphasise that 'first trimester' means exposure up to 13 completed weeks of pregnancy, but this certainly does not mean that all first trimester exposures occurred prior to 10 weeks i.e. during the period of organogenesis. In reality, a significant proportion of ondansetron exposures actually occurred *after* this period and thus any birth defects in the exposed group are unrelated to the exposure i.e. would have occurred anyway and were already there prior to the commencement of ondansetron therapy. Thus, a birth defect cannot necessarily be attributed to any exposure without accurate timing information and 'first trimester' is not a precise enough description of timing in this context.

In their data linkage study, Colvin et al.[11] while acknowledging the limitations of their data in terms of small sample size and large confidence intervals, reported a 20% increased risk of a major birth defect in babies exposed to ondansetron 'in the first trimester.' However, the mean gestational age of the first dispense during pregnancy was 11.9 weeks (±6.5 weeks) implying that a significant number of pregnancies would have only had exposure *after* embryogenesis. Only 10 birth defects were reported with 'first trimester use' and there was no information about the specific malformations identified in these cases.

Danielsson et al.[24] used data from the Swedish Medical Birth Register in the period 1998–2012 combined with the Swedish Register of Prescribed Drugs to identify 1349 infants born to women who had taken ondansetron in early pregnancy and the presence of birth defects was identified with 3 national health registers. Overall there was no statistically increased risk for major malformations, but there was an increased risk for cardiovascular defects (OR 1.62, 95% CI 1.04–2.14) and specifically cardiac septal defects (OR 2.05, 95%CI 1.19–3.28). In addition, only 899 cases were exposed prior to 10 weeks (i.e. during the period of organogenesis). Overall 19 infants in this study were identified with a cardiovascular defect, of which 17 had either a ventricular or atrial septal defect. The authors also pointed out that there is an excess of female infants born to mothers with NVP and this could also confound the data as there is also a female excess with regard to congenital cardiac defects.

Danielsson et al. postulated that the cardiac teratogenicity of ondansetron could be related to the drug's potential to prolong the QT interval, thereby causing embryonic cardiac arrhythmia resulting in reduced blood and oxygen supply to the developing heart and causing reperfusion damage including septal defects as a consequence. They cite this mechanism as a possible explanation for the potential cardiac teratogenicity seen with other drugs that cause cardiac arrhythmias or which alter the QT interval including erythromycin, phenytoin and clomipramine.

There is also a potential confounder in terms of the severity of the underlying condition being treated and whether the metabolic/fluid derangements associated with severe NVP could influence rates of birth defects or other adverse pregnancy outcomes rather than the treatment itself. Better studies to address this issue would need to include disease- matched controls exposed to other (or no) treatment for NVP as well as unexposed/non-NVP controls.

Some studies have attempted to address the issue of severity of NVP, by evaluating factors such as hospitalisation for NVP and use of other antiemetics.[23] In one study at least, severe NVP did not seem to increase risks, which is consistent with the notion that NVP correlates with a well-functioning placenta and thus better pregnancy outcomes.

Further muddying the waters is the fact that the vast majority of women with NVP, and particularly those with severe symptoms,

generally take numerous medications and therefore the ondansetron is part of a polypharmacy and polytherapy regimen, making it extremely difficult to attribute adverse outcomes to any single agent.

Given the paucity of details about the pregnancy outcomes and malformations reported in many of these studies, it is also very difficult to assess the severity and clinical significance of these defects and thus contextualise the risks in a meaningful way for both patients and their health care providers.

Some factors that can affect estimates of rates of birth defects include recall and ascertainment bias, the length of follow-up from birth, specific surveillance of exposed infants and whether or not prenatally diagnosed anomalies (which may result in termination of pregnancy) are included.

Given that the data in most retrospective case control studies is obtained by interviews or questionnaires administered to mothers months or even years after the birth of an affected child, there may well be significant recall bias regarding the nature and timing of exposure early in a pregnancy that may have occurred several years previously. This time-lag may be critical in terms of attributing a defect to an exposure which could well have occurred after the critical period of organogenesis. It is also well-recognised that mothers of babies with or without birth defects may have inaccurate recollection of medication usage during the critical period of embryonic development.

Likewise other studies have shown that because of heightened concerns, women with anxiety and depression exposed to medications such as SSRIs are more likely to have ultrasounds and cardiac echocardiography performed in their babies and to attend outpatient departments and, thus, there will be an increased opportunity to detect murmurs and small asymptomatic defects such as VSDs which may well go undetected in a baby not exposed to the medication. This phenomenon could also apply to a drug like ondansetron, especially when there is heightened public awareness of potential risks raised in the media and online and also in the approved Product Information.[26]

It is important that decisions weighing up therapeutic options to manage severe NVP are made by women and their health care providers based on clinical context and with a clear understanding of the quality and limitations of the data on which their decisions are made.

Even though the data is somewhat conflicting and certainly does not suggest a significantly increased risk of cardiac or other structural defects the following statements would seem reasonable from a purely pragmatic standpoint

1. Ondansetron should not be used as first line treatment of NVP at *any* stage of pregnancy
2. In those women with intractable symptoms of NVP (HG) in the first trimester of pregnancy, ondansetron may well offer significant improvement in quality of life and ability to function and therapy should be initiated with an understanding that the risks of teratogenicity do not appear to be significantly increased above the background risk (of 3–5%). It is important that risk factors for serotonin syndrome and prolongation of QT interval or torsade de pointes are excluded, particularly any potential risk arising from concurrent use of medications known to increase these risks.
3. Commencement of treatment after 10 weeks of gestation i.e. after embryonic development is completed, minimises risks of teratogenicity and would be advised for the majority of women with NVP who require treatment after other therapeutic options have been unsuccessful or inadequate.

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